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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/523,809	03/13/2000	Michael P. Murphy	686.03.498CON	6553

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EXAMINER	
KAUSHAL, SUMESH	

ART UNIT	PAPER NUMBER
1636	

DATE MAILED: 03/10/2004

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	09/523,809	MURPHY ET AL.	
	Examiner	Art Unit	
	Sumesh Kaushal Ph.D.	1636	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *13 November 2003*.

2a)☐ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *31-52* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *31-52* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: _____.

DETAILED ACTION

Applicant's response filed on 11/13/03 has been acknowledged.

Claims 1-30 are canceled.

Claims 31-52 are newly filed.

Claims 31-52 are pending and are examined in this office action.

*Applicants are required to follow Amendment Practice under revised **37 CFR §1.121.** The fax phone numbers for the organization where this application or proceeding is assigned is **703-872-9306**.*

Continued Examination Under 37 CFR 1.114

A request for continued examination under 37 CFR 1.114, including the fee set forth in 37 CFR 1.17(e), was filed in this application after final rejection. Since this application is eligible for continued examination under 37 CFR 1.114, and the fee set forth in 37 CFR 1.17(e) has been timely paid, the finality of the previous Office action has been withdrawn pursuant to 37 CFR 1.114. Applicant's submission filed on 11/13/04 has been entered.

Claim Rejections - 35 USC § 112

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 31-52 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the enablement requirement. The claim(s) contains subject matter which was not described in the specification in such a way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention.

Nature of Invention:

Invention relates to an artificial skin construct.

Breadth of Claims and Guidance Provided in the Specification

The scope of instant claims encompasses:

A cultured skin construct having at least two layers, comprising: a) a first layer of cultured dermal fibroblast cells which produce a layer of extracellular matrix in the absence of exogenous matrix components during the culturing conditions *(any and all: growth factor and culture conditions not defined)*; and (b) a second layer of keratinocyte cells disposed on the first layer to form an epidermal cell layer, wherein the epidermal cell layer is multilayered, stratified, differentiated and exhibits a basal layer, suprabasal layer, a granular layer and a stratum corneum; and wherein the bilayered cultured skin construct has a basement membrane present at the junction of the first and second layers (*wherein the keratinocyte cells makes an epidermal layer (as claimed) under any and all culture conditions: i.e. growth factors and culture conditions).*

A cultured skin construct having at least two layers, comprising: a) a first layer of cultured dermal fibroblast cells which produce a layer of extracellular matrix in the absence of exogenous matrix components during the culturing conditions *(any and all: growth factor and culture conditions not defined)*; and (b) a second layer of keratinocyte cells disposed on the first layer to form an epidermal cell layer *wherein the keratinocyte cells makes an epidermal layer (as claimed) under any and all culture conditions: i.e. growth factors and culture conditions).*

A cultured skin construct having at least three layers, comprising: a) a first layer of cultured dermal fibroblast cells which produce a layer of extracellular matrix in the absence of exogenous matrix components during the culturing conditions *(any and all: growth factor and culture conditions not defined)*; and (b) a second layer of keratinocyte cells disposed on the first layer to form an epidermal cell layer (*wherein the keratinocyte cells makes an epidermal layer (as claimed) under any and all culture conditions: i.e. growth factors and culture conditions)* c) and a third layer of cells deposed on the second layer.

In addition the scope of invention as claimed encompasses method of producing and using the above mentioned skin construct for transplantation or implantation into a patient.

Even though the specification teaches optimization of culture conditions for human fibroblasts to produce a layer of extracellular matrix in the absence of exogenous matrix components (see spec. Examples 1, 3 and 15), the specification fails to disclose what are the culturing conditions i.e. culture media contents, growth factors, culture environment that leads to the synthesis of (i) type I and type III collagen, (ii)

decorin, (iii) fibronectin, (iv) tenascin, and, (v) glycosaminoglycans. Specifically, the specification fails to disclose a culturing condition (culture media contents, growth factors, culture environment) in which the fibroblast cells when cultured produce type I and type III collagens (as claimed) and tenascin. The specification fails to identify type I and type III collagens (as claimed) and tenascin in the extracellular matrix secreted by cultured fibroblasts. In addition the specification fails to disclose that fibroblast cells derived form tissues selected from form tendon, lung, cartilage, urethra, corneal stroma, oral mucosa, umbilical cord, and intestine are capable of synthesizing extracellular components (as claimed) under any and all culture conditions. Regarding formation of an epidermal layer the specification only disclosed the use of a specific culture conditions, which comprises culturing the seeded keratinocytes in an epidermalization medium followed by culturing of the skin construct under submerged conditions (air-liquid interface) in a culture media that is different from the epidermalization medium (Spec. page 46, example-16). The specification fails to disclose that use of any and all culture conditions (i.e. culture media contents, growth factors, culture environment) would lead to the formation of an epidermal layer (as claimed) in a cultured skin construct.

State of Art and Predictability

The state of the tissue engineering art at the time of filing teaches that to engineer living tissues in vitro, cultured cells are coaxed to grow on bioactive degradable scaffolds that provide the physical and chemical cues to guide their differentiation and assembly into three-dimensional tissues. The assembly of cells into tissues is a highly orchestrated set of events that requires time scales ranging from seconds to weeks and dimensions ranging from 0.0001 to 10 cm. Coaxing cells to form tissues in a reliable manner is the quintessential engineering design problem that must be accomplished under the classical engineering constraints of reliability. Even though fewer than five engineered tissues have been approved, there are still many technical challenges to overcome before an "off-the-shelf" tissue could be created that represent the translation of scientific discoveries into treatments for patients. Furthermore, the successful large-scale production of engineered tissues requires an adequate source of

healthy expandable cells, the optimization of scaffolds, and the creation of bioreactors, which mimic the environment of the body and that are amenable to scale-up. Additional challenges include the preservation of the product so that it has a long shelf-life and the successful use of various approaches to prevent tissue rejection (Naughton et al Science 295:1009-1014, 2002).

Under the law Limitations appearing in the specification but not recited in the claim are not read into the claim. In re Prater, 415 F.2d 1393, 1404-05, 162 USPQ 541, 550-551 (CCPA 1969). See also In re Zletz, 893 F.2d 319, 321-22, 13 USPQ2d 1320, 1322 (Fed. Cir. 1989). Furthermore, claims are interpreted in light of the specification does not mean that everything in the specification must be read into the claims. Raytheon Co. v. Roper Corp., 724 F.2d 951, 957, 220 USPQ 592, 597 (Fed. Cir. 1983), cert. denied, 469 U.S. 835 (1984). See also MPEP § 2111 - § 2111.01.

In instant case the invention as claimed encompasses multi-layered cultured skin construct comprising a layer of cultured dermal fibroblast cells which produce a layer of extracellular matrix in the absence of exogenous matrix components during any and all culturing conditions. The instant claims fail to recite what are the culturing conditions for example culture media contents, growth factors, culture environment that leads to the synthesis of the claimed extracellular matrix components (I and type III collagens, decorin, fibronectin, tenascin and any and all glycosaminoglycans to support the growth and proliferation of second layer of epithelial cells. Similarly the instant claims fail to recite what are the culturing conditions (culture media contents, growth factors, culture environment that leads to the formation of epidermis during any and all culturing conditions.

Under the law, the disclosure "shall inform how to use, not how to find out how to use for themselves." See In re Gardner 475 F.2d 1389, 177 USPQ 396 (CCPA 1973).
At issue, under the enablement requirement of 35 U.S.C. 1 12, first paragraph is whether, given the Wands factors, the experimentation was undue or unreasonable under the circumstances. "Experimentation must not require ingenuity beyond that to be expected of one of ordinary skill in the art." See Fields v. Conover, 443 F.2d 1386, 170 USPQ 276 (CCPA 1970). In instant case making a multi-layered cultured skin construct

under any and all culture conditions (culture media contents, growth factors, culture environment) is not routine in the art and without sufficient guidance to a specific culture conditions the experimentation left to those skilled in the art is unnecessarily, and improperly, extensive and undue. See In re Wands 858 F.2d 731, 8 USPQ2nd 1400 (Fed. Cir, 1988).

Claim Rejections - 35 USC § 102

The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless –
> (b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

Claims 31-32, 36-38, 48-49 are rejected under 35 U.S.C. 102(b) as being anticipated by Fleishmajer et al (J. Histochem Cytochem 41(9):1359-66, 1993).

The instant claims are drawn to a cultured skin construct having at least two layers, comprising: a first layer of cultured dermal fibroblast cells which produce a layer of extracellular matrix and a second layer of keratinocyte cells disposed on the first layer to form an epidermal cell layer, wherein the epidermal cell layer is multilayered, stratified, differentiated and exhibits a basal layer, suprabasal layer, a granular layer and a stratum corneum; and wherein the bilayered cultured skin construct has a basement membrane present at the junction of the first and second layers.

Fleishmajer et al teaches a keratinocytes-fibroblast co-culture model for reconstruction of human skin (see claims 31-32, 36-38). Regarding claims 48-49 the cited art teaches an isolation of fibroblast and keratinocytes from human neonatal foreskin. The cited art further teaches fibroblasts were seeded onto a nylon mesh (in the absence of an extracellular matrix) and were kept in culture for 26 days in a chemically defined medium comprising DMEM containing 10% calf serum and 100ug/ml ascorbic

acid. The cited art further teaches that at the end of culture the fibroblasts were embedded I a rich extracellular matrix that closely resembles the in vivo situation. The cited art further teaches that keratinocytes were seeded onto the dermal substrate comprising the cultured fibroblasts and grown submerged for one week, followed by second growth period in a air-liquid interface in a second culture medium comprising DMEM containing 5% FCS, 100 ug/ml ascorbate and 0.5ug/ml hydrocortisone (page 1359, col.2 para.2). In addition the cited art teaches that the keratinocytes-fibroblast co-culture model express extracellular matrix components: Type-I and Type-II collagen, Decorin (a glycosaminoglycan), Fibronectin and Tenascin (page 1365, table-I). Regarding claim 31 the cited art further teaches that keratinocytes-fibroblast co-culture model forms a basal lamina (basement membrane) at the junction between the keratinocytes layer and fibroblast cells comprising type-IV collagen, laminin, nidogen and heparan sulfate (page 1362, col.2, para.1). Thus the cited art clearly anticipate the invention as claimed.

Claim Rejections - 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

Claims 33-35, 39-47 and 50-52 rejected under 35 U.S.C. 103(a) as being unpatentable over Fleishmajer et al (J. Histochem Cytochem 41(9):1359-66, 1993) as applied to claims 31-32, 36-38, 48-49 above, and further in view of Naughton et al (US 5,266,480, 1993).

Claims 39-47 are drawn to a cultured skin construct having at least three layers, comprising: a first layer of cultured dermal fibroblast cells which produce a layer of

extracellular matrix and a second layer of epithelial cells (keratinocytes) disposed on the first layer to form an epidermal cell layer, and a third layer of cells diposed on the second layer of epithelial cells. Claims 34-35 and 44-45 are drawn to fibroblast cells that are genetically engineered. Claims 33 and 42 are further drawn to a skin construct containing dermal papilla of hair follicles. Claims 50-52 are drawn to a method for transplantation or implantation of cultured skin construct in a patient.

Fleishmajer et al teaches a keratinocytes-fibroblast co-culture model for reconstruction of human skin (see claims 31-32, 36-38). Regarding claims 48-49 the cited art teaches an isolation of fibroblast and keratinocytes from human neonatal foreskin. The cited art further teaches fibroblasts were seeded onto a nylon mesh (in the absence of an extracellular matrix) and were kept in culture for 26 days in a chemically defined medium comprising DMEM containing 10% calf serum and 100ug/ml ascorbic acid. The cited art further teaches that at the end of culture the fibroblasts were embedded I a rich extracellular matrix that closely resembles the in vivo situation. The cited art further teaches that keratinocytes were seeded onto the dermal substrate comprising the cultured fibroblasts and grown submerged for one week, followed by second growth period in a air-liquid interface in a second culture medium comprising DMEM containing 5% FCS, 100 ug/ml ascorbate and 0.5ug/ml hydrocortisone (page 1359, col.2 para.2). In addition the cited art teaches that the keratinocytes-fibroblast co-culture model express extracellular matrix components: Type-I and Type-II collagen, Decorin (a glycosaminoglycan), Fibronectin and Tenascin (page 1365, table-I). Regarding claim 31 the cited art further teaches that keratinocytes-fibroblast co-culture model forms a basal lamina (basement membrane) at the junction between the keratinocytes layer and fibroblast cells comprising type-IV collagen, laminin, nidogen and heparan sulfate (page 1362, col.2, para.1).

However Fleishmajer does not teaches a third layer of cells deposited on the second layer of epithelial cells. In addition Fleishmajer does not teaches genetic motification of cell in keratinocytes-fibroblast co-culture model or a skin construct containing a dermal papilla of hair follicles.

Naughton et al teaches a three-dimensional skin culture system. Regarding claims 34-35 and 44-45 (genetically engineered cells) the cited art teaches genetic modification of cells used in the three-dimensional culture system to produce a foreign gene product selected from a growth factor, regulatory factor, peptide, hormone, antibody etc (co.20 lies 54-62).

Regarding claim 39-41 and 43-47 (three layered skin construct) the cited art teaches a culture of isolated fibroblasts was established on a nylon mesh, which resulted in the adherent and growth of fibroblasts into the meshwork. The cited art teaches that these fibroblasts were metabolically active, secreted an extracellular matrix, and rapidly formed a dermal equivalent consisting of active fibroblasts and collagen (type I any type III) see col.44 lines 20-35. The cited art further teaches that melanocytes (second layer) were plated on to the fibroblast coated nylon mesh and allowed to grow for 3 days prior to the addition of keratinocytes (third layer) see col.45 lines 1-14. In addition the cited art teaches that other types of cells that may be used to inoculate the three-dimensional matrix include endothelial cells, pericytes, macrophages, monocytes, lymphocytes, plasma cells adipocytes etc (col. 30 line 53-59).

Regarding claim 33 and 42 (hair follicles) the cited art teaches three-dimensional skin culture system may include introduction of a hair follicles and associated glands into the transplant site. The cited art further teaches implantation of skin-constructs containing hair follicles thereby creating a transplanted site, which is histologically normal and functionally similar to the normal skin (col.31, lines 44-59).

Regarding claims 50-52 (method of transplanting) the cited art teaches a method for transplantation or implanting of cultured skin construct in-vivo (col.45, line 40). The cited art teaches transplantation of skin construct in experimental rats, wherein meshes with dermal and epidermal components were implanted into 10mmx10mm skin biopsies. The cited art further teaches that these engraftment studies suggested that the three-dimensional skin matrix system mimics a true physiological system in which all cell components are activated and natural growth factors are being produced (col. 46 lines 8-24).

Thus it would have been obvious to one ordinary skill in the art at the time of filing to modify the teaching of Fleishmajer by substituting fibroblasts with genetically engineered fibroblast cells in view of Naughton. One would have been motivated to do so to produce recombinant protein in the skin construct (bioreactor system).

Furthermore, it would have been obvious to one ordinary skill in the art to modify the skin construct of Fleishmajer by incorporating dermal papilla of hair follicles in view of Naughton. One would have been motivated to do so induce hair growth at site of skin implant.

In addition a method for transplantation or implantation of a skin construct as taught by Fleishmajer is obvious in view of Naughton who teaches the technique of skin biopsies and transplantation. On would have been motivated to do so to promote wound healing in transplanted patients.

One would have a reasonable expectation of success in doing so because genetic engineering of fibroblast host cells, substitution of a cell type in a skin construct and transplantation of skin construct is not only well within the reach of one ordinary skill in the art but also has been routine in the art.

The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

Claims 32, 36, 43, 47 and 48 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

Claim 32 and 43 recites claim limitation “chemically defined media”. It is unclear what encompasses a chemically defined media in this context. For example it is unclear what are the ingredients of such media.

Claim 36 and 47 recites claim limitation “tissue-like handling”. It is unclear what are tissue-like handling properties in this context (besides having physical unitary).

Claim 48 is indefinite because the claim recites claim limitation "stimulating the fibroblast cells to synthesize, secrete and organize extracellular matrix components in a second culture medium". It is unclear what comprises "second culture media" that stimulates fibroblast cells to synthesize the claimed extracellular matix components.

MPEP 2173.05(q) clearly states that attempts to claim a process without setting forth any steps involved in the process generally raises an issue of indefiniteness under 35 U.S.C. 112, second paragraph. For example, a claim which read: "A process for using monoclonal antibodies of claim 4 to isolate and purify human fibroblast interferon." was held to be indefinite because it merely recites a use without any active, positive steps delimiting how this use is actually practiced.Ex parte Erlich, 3 USPQ2d 1011 (Bd. Pat. App. & Inter. 1986). Other decisions suggest that a more appropriate basis for this type of rejection is 35U.S.C. 101. In Ex parte Dunki, 153 USPQ 678 (Bd. App. 1967), the Board held the following claim to be an improper definition of a process: "The use of a high carbon austenitic iron alloy having a proportion of free carbon as a vehicle brake part subject to stress by sliding friction." In Clinical Products Ltd. v. Brenner, 255 F. Supp. 131, 149 USPQ 475 (D.D.C. 1966), the district court held the following claim was definite, but that it was not a proper process claim under 35 U.S.C. 101: "The use of a sustained release therapeutic agent in the body of ephedrine absorbed upon polystyrene sulfonic acid." Although a claim should be interpreted in light of the specification disclosure, it is generally considered improper to read limitations contained in the specification into the claims. See In re Prater, 415 F.2d 1393, 162 USPQ 541 (CCPA 1969) and In re Winkhaus, 527 F.2d 637, 188 USPQ 129 (CCPA 1975), In re Van Guens, 988 F.2d 1181, 26 PSPG2d 1057 (Ded. Cir. 1991), which discuss the premise that one cannot rely on the specification to impart limitations to the claim that are not recited in the claim. Accordingly, without the recitation of all these critical limitations, the claims do not adequately define the instant invention.

Conclusion

No claims are allowed.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Sumesh Kaushal Ph.D. whose telephone number is 571-272-0769. The examiner can normally be reached on Mon-Fri. from 9AM-5PM. If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Yucel Irem Ph.D. can be reached on 571-272-0781.

The fax phone number for the organization where this application or proceeding is assigned is **703-872-9306**. Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

Sumesh Kaushal
Examiner Art Unit 1636

JAMES KETTER
PRIMARY EXAMINER